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AB BACKGROUND: Molecules that are highly expressed by human prostate cancers may serve as therapeutically relevant targets or tumor markers. Tyrosine kinases are frequently overexpressed in **metastatic** tumor cells and this prompted us to screen for tyrosine kinases that are overexpressed in prostate cancer cells. METHODS: Expression levels of the **EphA2** receptor tyrosine kinase were determined by Western blot analysis in canine and human prostate cancer cell lines and in immortalized and transformed variants of 267B1 prostatic epithelial cells. **EphA2** levels in benign human prostate and prostate cancers were also determined in formalin-fixed, paraffin-embedded tissues using immunohistochemical staining. RESULTS: **Metastatic** prostate cancer cells overexpressed **EphA2** by 10-100 fold as compared with non-invasive prostatic epithelial cells. **EphA2** immunoreactivity in vivo was also significantly greater in human prostate cancers as compared with benign prostate epithelium. CONCLUSIONS: The **EphA2** receptor tyrosine kinase is differentially expressed in human and canine prostate cancer cell lines and overexpressed in human prostate cancers as compared with benign prostate tissues. **Metastasis**-derived canine prostate carcinoma cell lines overexpress **EphA2** and may provide pre-clinical models to further evaluate the role of **EphA2** in prostate carcinogenesis. Further investigations are needed to determine the utility of **EphA2** as a tumor marker and a novel target in human prostate cancer.